



**[Billing Code 4140-01-P]**

## **DEPARTMENT OF HEALTH AND HUMAN SERVICES**

### **Evaluation of an Up-and-Down Procedure for Acute Dermal Systemic Toxicity Testing: Request for Nominations for an Independent Expert Panel and Submission of Relevant Data**

**AGENCY:** Division of the National Toxicology Program (DNTP), National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH).

**ACTION:** Request for Data; Request for Nominations of Scientific Experts

**SUMMARY:** The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), in collaboration with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), is planning to convene an independent scientific peer review panel (Panel) to assess the validation status of an up-and-down procedure (UDP) for acute dermal systemic toxicity testing. NICEATM requests nominations of scientific experts who can be considered for the Panel and submission of data for substances tested in *in vivo* acute dermal and oral systemic toxicity tests.

**DATES:** Nominations and test method data for the acute dermal and oral tests should be submitted by [insert date 45 days from publication]. Data submitted after this date will be considered in the evaluation where feasible.

**FOR FURTHER INFORMATION CONTACT:** Dr. William S. Stokes, Director, NICEATM, NIEHS, P.O. Box 12233, Mail Stop: K2-16, Research Triangle Park, NC, 27709, (telephone)

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NICEATM, NIEHS, Room 2034, 530 Davis Drive, Morrisville, NC 27560.

## **SUPPLEMENTARY INFORMATION:**

### **Background**

Acute poisoning from chemicals and chemical products, including pharmaceuticals, is a significant public health problem. In 2009, 2.5 million human poisoning cases were reported to U.S. poison control centers (Bronstein *et al.*, 2010). Dermal exposures were involved in 7.25% (179,832 cases) of the poisonings, which was second in frequency only to exposures by oral ingestion (2,080,781 cases). To protect workers and consumers from acute dermal poisoning exposures, regulatory agencies in the U.S. (e.g., the Environmental Protection Agency [EPA], the Consumer Products Safety Commission, Department of Transportation, Occupational Safety and Health Administration) use the information from acute dermal systemic toxicity tests using rabbits or rodents to determine the potential of chemicals and chemical products to cause life-threatening health effects or death from acute dermal exposures. Test results are used as the basis for hazard classification and labeling and to inform consumers and workers how to avoid acute dermal exposures to hazardous chemicals and products during the handling, transport, and use of chemicals and products.

In 2002, ICCVAM recommended the revised UDP for acute oral systemic toxicity as a replacement for the conventional test. The revised oral UDP was accepted internationally as Organisation for Economic Co-operation and Development (OECD) Test Guideline 425 in 2001 (OECD, 2001). The oral UDP reduces animal use by up to 70% compared to the traditional testing procedure. NICEATM is now developing a UDP procedure for acute dermal systemic toxicity testing, which is one of the four most commonly conducted product safety tests

worldwide. Alternative test methods for acute dermal systemic toxicity testing are an ICCVAM priority because such testing is required by multiple agencies, can involve large numbers of animals, and can result in significant pain and distress to test animals (ICCVAM, 2008).

The acute dermal systemic toxicity UDP protocol is expected to reduce the number of animals used compared with current EPA (EPA, 1998) and OECD (OECD, 1987) test guidelines. A draft background review document (BRD) will include a proposed dermal UDP test method protocol and analyses comparing the results of simulated testing using the UDP protocol with the standard acute dermal systemic toxicity reference test described in EPA Health Effects Test Guidelines OPPTS 870.1200 (EPA, 1998) and OECD Test Guideline 402 (OECD, 1987). The draft BRD will form the basis for the ICCVAM draft test method recommendations for the proposed UDP method. Draft recommendations on usefulness and limitations, standardized test method protocol, and future studies will be provided to the Panel and made available to the public.

The Panel will meet in public session to review the validation status of the UDP for acute dermal systemic toxicity testing. The Panel will comment on the extent to which the BRD supports the draft ICCVAM test method recommendations. Meeting information, including dates, locations, and public availability of the meeting documents will be announced in a future **Federal Register** notice and will also be posted on the NICEATM–ICCVAM website (<http://iccvam.niehs.nih.gov>).

### **Request for Nominations of Scientific Experts**

NICEATM requests nominations of scientists with relevant knowledge and expertise to serve on the Panel. Areas of relevant expertise include, but are not limited to biostatistics; human and veterinary dermatology, with an emphasis on evaluation and treatment of chemical

injuries that produce systemic effects; human and animal toxicology, especially systemic effects due to dermal exposures; *in vivo* dermal and oral toxicity testing; and test method validation. Each nomination should include the nominee's name, affiliation, contact information (i.e., mailing address, email address, telephone and fax numbers), *curriculum vitae*, and a brief summary of relevant experience and qualifications.

### **Request for Data**

NICEATM invites the submission of data for substances tested in standardized *in vivo* acute dermal systemic toxicity tests. Corresponding acute oral LD<sub>50</sub> data for the same compounds tested dermally would be particularly useful. Oral data from rat tests and dermal data from rat and/or rabbit tests are preferred. Although data can be accepted at any time, please submit data by [insert date 45 days from publication] to ensure consideration during the ICCVAM evaluation process. Relevant data received after this date will be considered where feasible. All information submitted in response to this notice will be made publicly available and may be incorporated into future NICEATM and ICCVAM reports and publications, as appropriate.

When submitting data, please reference this **Federal Register** notice and provide appropriate contact information (name, affiliation, mailing address, phone, fax, email, and sponsoring organization, as applicable). NICEATM prefers that data be submitted electronically as copies of pages from study notebooks, spreadsheets, and/or study reports. Each submission for a substance should preferably include the following information, as appropriate: common and trade name, Chemical Abstracts Service Registry Number (CASRN), commercial source, *in vivo* test protocols used, extent to which the data were collected in accordance with national or international Good Laboratory Practice guidelines, date and testing organization, physical and

chemical properties (e.g., molecular weight, pH, water solubility, log K<sub>ow</sub>, etc.), estimated LD<sub>50</sub>, and incidence of death and other adverse effects.

### **Background Information on ICCVAM and NICEATM**

ICCVAM is an interagency committee composed of representatives from 15 Federal regulatory and research agencies that require, use, generate, or disseminate toxicological and safety testing information. ICCVAM conducts technical evaluations of new, revised, and alternative safety testing methods and integrated testing strategies with regulatory applicability and promotes the scientific validation and regulatory acceptance of testing methods that more accurately assess the safety and hazards of chemicals and products and that reduce, refine (enhance animal well-being and lessen or avoid pain and distress), or replace animal use. The ICCVAM Authorization Act of 2000 (42 U.S.C. 285l–3) established ICCVAM as a permanent interagency committee of the NIEHS under NICEATM. NICEATM administers ICCVAM, provides scientific and operational support for ICCVAM-related activities, and conducts independent validation studies to assess the usefulness and limitations of new, revised, and alternative test methods and strategies. NICEATM and ICCVAM welcome the public nomination of new, revised, and alternative test methods and strategies for validation studies and technical evaluations. Additional information about NICEATM and ICCVAM can be found on the NICEATM–ICCVAM website (<http://iccvam.niehs.nih.gov>).

### **References**

Bronstein AC, Spyker DA, Cantilena LR, Jr, Green JL, Rumack BH, Giffin SL. 2010. 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 27th Annual Report. *Clinical Toxicology* 48: 979–1178.

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ICCVAM. 2008. NICEATM-ICCVAM Five-Year Plan (2008-2012): A Plan to Advance Alternative Test Methods of High Scientific Quality to Protect and Advance the Health of People, Animals and the Environment. Research Triangle Park, NC:National Institute of Environmental Health Sciences. Available: <http://iccvam.niehs.nih.gov/docs/5yearplan.htm>.

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OECD. 2001. Test No. 425. Acute Oral Toxicity - Up-and-Down Procedure [adopted 17 December 2001]. In: OECD Guidelines for the Testing of Chemicals, Section 4: Health Effects. Paris:OECD Publishing. Available: [www.oecd.org/dataoecd/17/51/1948378.pdf](http://www.oecd.org/dataoecd/17/51/1948378.pdf).

Dated: July 12, 2012

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[FR Doc. 2012-17787 Filed 07/20/2012 at 8:45 am; Publication Date: 07/23/2012]